REMARKS

Status of the Claims

Claims 1-34 and 44-47 are currently pending in the present application. By this paper, claims 24-27, 29-33, 45, and 46 are amended. New claims 48-50 are introduced. Consideration of claims 1-34 and 44-50 is respectfully requested in view of the foregoing remarks and amendments presented.

Applicant thanks the Examiner for clarifying by telephone to Applicant's representative Charlton Shen that the present office action is non-final as indicated on the summary page and is not final as indicated on page 23 of the Office Action.

Amendments to the Claims

New independent claim 48 recites a method that includes administering a pre-photosensitizing agent to epithelial tissue and a targeted tissue underlying the epithelial tissue, preventing metabolism of the pre-photosensitizing agent in the epithelial tissue, while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent in the targeted tissue, and irradiating the epithelial tissue and the targeted tissue, with the targeted tissue at a temperature in a range between about 25°C and about 40°C during the irradiation, to activate the photosensitizing agent in the targeted tissue without substantially affecting the epithelial tissue.

New claim 49 depends on claim 48 and recites that the epithelial tissue and the targeted tissue are irradiated with the epithelial tissue at a temperature that is less than the temperature of the targeted tissue.

New independent claim 50 recites a method that includes administering a pre-photosensitizing agent to epithelial tissue and a targeted tissue underlying the epithelial tissue, applying a chemical inhibitor to prevent metabolism of the pre-photosensitizing agent in the epithelial tissue while allowing metabolism of the pre-photosensitizing agent in the targeted tissue, and irradiating the epithelial tissue and the targeted tissue. Support for these amendments can be

found throughout the present application, for example in originally filed claims 1, 17, and 23 and at paragraphs [0028] and [0033] of the Published Application.

Claims 24-27, 29-33, 45, and 46 are amended to depend from new claim 50.

No new matter is added.

Applicant respectfully requests entry of these amendments.

Nonobviousness

The Examiner rejects claims 1-19, 22, 44, and 47 pursuant to 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 6,050,990 (herein "Tankovich") in view of U.S. Patent No. 5,709,654 (herein "Klatz"). Claims 20 and 21 stand rejected under 35 U.S.C. §103(a) as being obvious over Tankovich in view of Klatz as applied to claim 1, and in further view of U.S. Patent No. 5,955,490 to Kennedy et al. (herein "Kennedy"). Claim 23, 25-34, 45, and 46 stand rejected under 35 U.S.C. §103(a) as being obvious over Tankovich in view of Klatz as applied to claim 1, and in further view of U.S. Patent No. 5,114,973 to Hess et al. (herein "Hess") and Kennedy. Claim 24 is rejected as being obvious over Tankovich in view of Klatz, Hess, and Kennedy as applied to claim 23, and further in view of U. S. Patent No. 5,763,235 to Wantanabe et al. (herein "Watanabe") The claims, however, are all patentable at least because the combination of art neither teaches nor suggests the claimed invention to one skilled in the art.

Independent Claim 1

Claim 1 recites a method that includes administering a pre-photosensitizing agent to epithelial tissue and a targeted treatment site underlying the epithelial tissue and preventing metabolism of the pre-photosensitizing agent in the epithelial tissue, while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent in tissue at the targeted treatment site. The method also includes irradiating the targeted treatment site to activate the photosensitizing agent at the targeted treatment site, wherein the epithelial tissue at the treatment site is substantially unaffected.

The Examiner argues on pages 3-4 of the Office Action argues that Tankovich discloses administering a pre-photosensitizing agent in the form of ALA to epithelial tissue at column 39, lines 58-66, which is clearly labeled as a discussion of hair removal Method No. 8 *using sunlight*. The Examiner also argues on pages 3-4 of the Office Action that Tankovich discloses creating a temperature gradient between epithelial tissue and a targeted treatment site at column 63, lines 59-61 and column 64, lines 58-67, which are portions of clearly labeled hair removal Method No. 22 *using a long pulse laser with skin cooling*. According to the Examiner on pages 5-6 of the Office Action, because Klatz teaches "that cooling tissue helps to protect it through lowering metabolism and slowing free radical production," it would have been obvious to combine the Method No. 8 application of ALA to skin and the Method No. 22 laser pulse irradiation of skin because "[a] skilled artisan would have recognized that it would be possible to prevent unwanted tissue damage by simply cooling the area surrounding the treatment site to prevent the metabolism of aminolevulinic acid [ALA] into a photosensitive compound before irradiating the area intended for treatment."

However, the Examiner continues to fail to provide a reason why a person of ordinary skill in the art would combine the separate sunlight and laser skin treatments methods disclosed in Tankovich. In the sunlight treatment, a pre-photosensitizing agent is presumably used because sunlight alone is not sufficient to provide the desired treatment. In the laser treatment, the skin cooling is provided presumably because the long wavelengths would otherwise unnecessarily damage the epithelial tissue. Thus, one skilled in the art practicing Tankovich's sunlight treatment would not want to diminish the effect of the sunlight by cooling the skin since the pre-photosensitizing agent was added to enhance the effect of the sunlight. As well, the skilled artisan would not want to use a photosensitizing agent with the long wavelength treatment since the laser already causes damage to the tissue. Accordingly, a skilled artisan would not have reason to combine these separate methods in Tankovich.

The *only* reason discussed in the Office Action for combining the sunlight and laser treatment methods disclosed in Tankovich is to "prevent the metabolism of a pre-photosensitizing agent in the upper layers of skin while allowing the metabolism in said lower layers" to "prevent unwanted tissue damage." Office Action, p.6 and 14. Such reasoning is gleaned directly and only

from Applicant's disclosure, using language from claim 1 no less. This is the definition of hindsight being used to impermissibly formulate a rejection of the claims.

To make a prima facie showing of obviousness of a claimed invention, the Examiner should "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*; *see* MPEP §2141, §2143.01(IV). Where no such explanation is given, as is the case here, improper use of hindsight can be inferred.

The Examiner argues on page 14 of the Office Action that Tankovich necessarily discloses preventing the metabolism of ALA in tissue in combination with cooling of the tissue because the skin naturally contains ALA. However, that is completely irrelevant to claim 1. Claim 1 requires administering *a pre-photosensitizing agent* to epithelial tissue and a targeted treatment site underlying the epithelial tissue, preventing metabolism of *the pre-photosensitizing agent* in the epithelial tissue, and irradiating the targeted treatment site to activate *the photosensitizing agent* at the targeted treatment site, wherein the epithelial tissue is substantially unaffected. As plainly seen, the only relevant pre-photosensitizing agent in claim 1 is the pre-photosensitizing agent administered to the tissue, not any hypothetical ALA that may be naturally present in the tissue.

The Examiner further argues on page 16 of the Office Action that "[t]he method of administering ALA does not require that a laser be utilized" and that "if a laser was utilized in order to target a specific site the amount of energy required from said laser would not be so high." However, this assertion of using a lower energy irradiating laser pulse does not dispute the fact that a laser pulse is damaging to skin, and indeed is the entire point of irradiating the skin with the laser, and that no person having ordinary skill in the art would combine the Method No. 8 application of ALA with the Method No. 22 laser irradiation because it would only increase chances of skin damage to unintended areas, namely epithelial tissue. Tankovich recognizes that the high energy laser pulse of Method No. 22 can damage the skin surface, which is why Tankovich teaches cooling that tissue to help prevent damage thereto. It would be nonsensical for a person having ordinary

skill in the art to increase sensitivity of the skin surface with ALA as in Method No. 8 only to decrease sensitivity of that skin surface as in Method No. 22, absent Applicant's disclosure.

It was Applicant, not Tankovich or Klatz, who recognized the benefit of administering a pre-photosensitizing agent to tissue *and* cooling the tissue.[1] As discussed in the present application (see paragraph [0004] of the Published Application), when a pre-photosensitizing agent is utilized in photodynamic therapy, the agent can be absorbed by both the epidermal tissue and dermal tissue, where the latter can be the tissue targeted for treatment. As a result, application of light can cause phototoxcity to the epidermis, which can lead to long-lasting hyperpigmentation or epidermal necrosis (see id.). Methods consistent with claim 1 potentially provide a solution to this problem. As disclosed in the present application through the description and examples therein, epithelial tissue can be protected when using PDT with a pre-photosensitizing agent by *preventing metabolism of the pre-photosensitizing agent in the epithelial tissue while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent in tissue at a targeted treatment site underlying the epithelial tissue* as recited in claim 1. It was Applicant, not Tankovich or Klatz, who acknowledges and addresses the problem.

While Applicant maintains the arguments in previously submitted papers regarding the lack of reason/motivation to combine the cited art and Klatz not remedying the deficiencies of Tankovich, such arguments are not necessary because a person having ordinary skill in the art would simply not combine the cited art in the suggested way to reach the claimed invention.

Accordingly, for at least these reasons, claim 1 is patentable over Tankovich and Klatz.

New Independent Claim 48

As mentioned above, claim 48 recites a method that includes administering a pre-photosensitizing agent to epithelial tissue and a targeted tissue underlying the epithelial tissue,

[1] Applicant notes that while the Examiner's rejection of claim 1 is predicated on cooling tissue, claim 1 does not recite cooling tissue. Claim 2, which depends from claim 1, recites creating a temperature gradient between the epithelial tissue and tissue at the targeted treatment site, but claim 1 only requires administering of a pre-photosensitizing agent to epithelial tissue and a targeted treatment site, preventing metabolism of the pre-photosensitizing agent in the epithelial tissue while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent in tissue at the targeted treatment site, and irradiating the targeted treatment site to activate the photosensitizing agent at the targeted treatment site, wherein the epithelial tissue is substantially unaffected.

preventing metabolism of the pre-photosensitizing agent in the epithelial tissue, while allowing the pre-photosensitizing agent to metabolize into a photosensitizing agent in the targeted tissue, and irradiating the epithelial tissue and the targeted tissue, with the targeted tissue at a temperature in a range between about 25°C and about 40°C during the irradiation, to activate the photosensitizing agent in the targeted tissue without substantially affecting the epithelial tissue.

None of the cited references, alone or in any combination, teach or suggest the recitation in claim 48 that the targeted tissue is at a temperature in a range between about 25°C and about 40°C during the irradiation. Claim 17, which depends from claim 1, includes a similar recitation and requires that the tissue at the targeted treatment site is heated to a temperature in the range of about 25° C to 40° C. In response to Applicant's argument regarding claim 17, the Examiner asserts on page 16 of the Office Action that Tankovich teaches heating tissue at the targeted treatment site to a temperature in the range of about 25° C to 40° C "because the targeted treatment site of Tankovich et al. is already between 25-40 degrees C (col. 63, last paragraph). Said treatment site is heated to body temperature, which is about 33 degrees C, by the body itself."

However, it is clear that ***during irradiation*** the targeted tissue in Tankovich is heated to a temperature *above* 40° C. Ambient body temperature of about 33 C° at the targeted treatment site is irrelevant. The targeted treatment site is at the site of the hair follicle desired to be damaged, surrounding the base of the hair duct, which Tankovich discloses is heated to about 70° C to 80° C. Col. 63, line 59 to col. 64, line 9; col. 64, lines 38-44; col. 65, lines 1-14; Fig. 32. Tissue at the targeted treatment site during irradiation in Tankovich is thus clearly above the temperature range recited in claim 48.

The Examiner indicates on page 16 of the Office Action that Tankovich heating tissue "to about 70 degrees in order to destroy the desired cells" does not matter because the tissue would not be heated to 70 degrees in a combination of Tankovich's Method Nos. 8 and 22. Specifically, the Examiner argues that "[t]hrough combination of the two methods, one would have been readily aware that the activation of ALA requires much less energy and that if a laser was utilized in order to target a specific site the amount of energy required from said laser would not be so high that the

energy from the laser itself would not heat the skin to 70 degrees." The Examiner is incorrect for at least two reasons.

First, it is clear that Tankovich does not teach irradiating the targeted treatment site at the recited temperature range. The Examiner presents no reference indicating that a laser would not heat the skin to 70 degrees as indicated and thus has not presented a prima facie case of obviousness.

Second, a person having ordinary skill in the art would not combine Method Nos. 8 and 22 in the first place, as discussed above regarding claim 1. As such, there is no teaching or suggestion in any of the cited references that during irradiation the targeted treatment site is at a temperature in a range between about 25°C and about 40°C.

Accordingly, for at least these reasons, claim 48 represents allowable subject matter.

New Independent Claim 50

As mentioned above, claim 50 recites a method that includes administering a pre-photosensitizing agent to epithelial tissue and a targeted tissue underlying the epithelial tissue, applying a chemical inhibitor to the epithelial tissue to prevent metabolism of the pre-photosensitizing agent in the epithelial tissue while allowing metabolism of the pre-photosensitizing agent in the targeted tissue, and irradiating the epithelial tissue and the targeted tissue.

With respect to claim 50, Applicant addresses the arguments the Examiner offered in the Office Action regarding claims 1 and 23.

In response to Applicant's argument that Tankovich, Klatz, Kennedy, and Hess, alone or in any combination, do not teach the recitation of claim 23, the Examiner provides one argument. On page 17 of the Office Action the Examiner asserts that "because one of ordinary skill in the art in the field of photo-dynamic therapy is readily aware of the mechanisms which take place in the body during treatment, including which compounds are photosensitive, what their synthetic pathways are, and what known chemicals may inhibit said pathways. One of ordinary skill in the art would have

been aware that several methods could be utilized in order to prevent metabolisms, including inhibitors and temperature reduction, in order to avoid treatment of non-treatment sites."

However, similar to that discussed above regarding claim 1, there is absolutely no reason why a person skilled in the art would apply a chemical inhibitor to tissue administered with a pre-photosensitizing agent. In lieu of such reasoning, the Examiner *assumes* it is known to prevent metabolism in tissue treated with a pre-photosensitizing agent and *then* follows with the argument that a person having ordinary skill in the art would use a chemical inhibitor to prevent such metabolism. That is classic impermissible hindsight reasoning using Applicant's disclosure as the basis for formulating a rejection, i.e., none of the references has even hinted at the notion of preventing metabolism of a pre-photosensitizing agent in epithelial tissue while allowing metabolism in the targeted tissue.

Kennedy is only relied on by the Examiner for a particular concentration of ALA, and Hess is only relied on to teach that succinylacetone is an inhibitor of ALA. But Hess, like Tankovich and Klatz, does not teach or suggest applying a chemical inhibitor to prevent metabolism of a pre-photosensitizing agent in epithelial tissue while allowing metabolism of the pre-photosensitizing agent in targeted. The fact that succinylacetone exists in the prior art does not bar patentability. The references simply do not, without Applicant's disclosure, provide any reason to administer a pre-photosensitizing agent to epithelial tissue *and* apply a chemical inhibitor to prevent metabolism of the pre-photosensitizing agent.

Accordingly, for at least these reasons, claim 50 represents allowable subject matter.

Dependent Claims 2-19, 22, 44, and 47

Claims 2-19, 22, 44, and 47 each depend ultimately from amended claim 1. Accordingly, each is patentable over the cited art at least for the same reasons that amended claim 1 is patentable. However, the dependent claims are also patentable for other independent reasons.

Claim 16

For example, claim 16 recites that tissue *at the targeted treatment site* is heated to a temperature that is equal to about 25° C. On page 4 of the Office Action the Examiner cites column 3, lines 40-54 of Tankovich as disclosing such a feature, but neither this portion nor any other portion of Tankovich discloses the claimed heating of tissue.

The portion of Tankovich at column 3, lines 40-54 clearly refers to the temperature of tissue at the *skin surface*, not at the targeted treatment site. As discussed above regarding claim 48, the irradiation in Tankovich heats tissue at the targeted treatment site to about 70° C to 80° C. That is clearly not equal to about 25° C.

Also similar to that discussed above regarding claim 48, ambient body temperature of about 33° C at the targeted treatment site is irrelevant. Applicant reminds the Examiner that claim 16 depends from claim 15, which depends from claim 2, which depends from claim 1. Claim 2 recites that the step of preventing metabolism of the pre-photosensitizing agent in epithelial tissue comprises creating a temperature gradient between the epithelial tissue and tissue at the targeted treatment site. Claim 15 recites that the temperature gradient is created by cooling the epithelial tissue *and heating tissue at the targeted treatment site*. Claim 16 is thus not directed to an ambient temperature of the targeted treatment site like the Examiner appears to be arguing. Rather, claim 16 requires that tissue at the targeted treatment site is *heated* to temperature that is equal to about 25° C, which is clearly not disclosed in Tankovich.

Claim 17

For another example, claim 17 recites that tissue *at the targeted treatment site* is heated to a temperature in the range of about 25° C to 40° C. Similar to that discussed above regarding claims 16 and 48, Tankovich does not teach or suggest such a recitation.

Claim 47

For another example, claim 47, which depends from claim 2, recites that the step of irradiating the targeted treatment site comprises maintaining at least a portion of the targeted

treatment site at a temperature in a range between about 25°C and about 40°C. As discussed above regarding claims 16 and 48, irradiation of the tissue at the targeted treatment site in Tankovich clearly heats the tissue to about 70° C to 80° C. The tissue at the targeted treatment site is thus not maintained at a temperature in a range between about 25°C and about 40°C.

Dependent Claims 20 and 21

At least for the reasons discussed above, Tankovich and Klatz do not make obvious independent claim 1. Kennedy is relied on only for dependent claim features, namely that the targeted treatment site can include malignant cells or sebaceous glands, and does not remedy the deficiencies of Tankovich and Klatz. Accordingly, claim 20-21 distinguish over Tankovich, Klatz, and Kennedy, either taken alone or together, and are allowable at least because they depend from an allowable base claim.

Dependent Claims 23, 25-34, 45, and 46 and New Dependent Claim 49

At least for the reasons discussed above, Tankovich, Klatz, Kennedy, and Hess do not make obvious independent claims 1 and 48. Accordingly, claim 23, 25-34, 45, 46, and 49 distinguish over Tankovich, Klatz, Kennedy, and Hess either taken alone or together, and are allowable at least because they depend from an allowable base claim. The claims, however, are also allowable for other independent reasons.

Claim 23

For example, claim 23 recites that the step preventing metabolism of the pre-photosensitizing agent in epithelial tissue comprises applying a chemical inhibitor to the epithelial tissue. As discussed above regarding independent claim 50, none of the cited references teach or suggest applying a chemical inhibitor to epithelial tissue to prevent metabolism of a pre-photosensitizing agent as part of a method for protecting epithelial tissue during photodynamic therapy. Accordingly, claim 23 is not obvious over the cited combination.

Dependent Claim 24

At least for the reasons discussed above, Tankovich, Klatz, Kennedy, and Hess do not make obvious independent claim 48. Watanabe is relied on only for a dependent claim feature, namely that the chemical inhibitor is at a concentration that is equal to about 0.1%, and does not remedy the deficiencies of Tankovich, Klatz, Kennedy, and Hess. Accordingly, claim 24 distinguishes over Tankovich, Klatz, Kennedy, Hess, and Wantanabe, either taken alone or together, and is allowable at least because it depends from an allowable base claim.

CONCLUSION

Applicant submits that all pending claims are in condition for allowance, and allowance thereof is respectfully requested. Applicant's amendment of the claims does not constitute a concession that the claims are not allowable in their unamended form. The Examiner is encouraged to telephone the undersigned attorney for Applicant if such communication is deemed to expedite prosecution of this application.

In the event that a petition for an extension of time is required to be submitted at this time, Applicant hereby petitions under 37 CFR §1.136(a) for an extension of time for as many months as are required to ensure that the above-identified application does not become abandoned.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 141449, under Order No. 22727-110.

Dated: April 3, 2009

Respectfully submitted,

By: /Christina M. Sperry/
Christina Sperry
Registration No.: 47,109
NUTTER MCCLENNEN & FISH LLP
World Trade Center West
155 Seaport Boulevard
Boston, Massachusetts 02210-2604
(617) 439-2394
(617) 310-9394 (Fax)
Attorney for Applicant

1804570.1